

REMARKS

1. Status of the Claims

Claim 1 is cancelled.

Claims 3-5 and 7-11 are amended to depend on claim 2. Support for these amendments can be found in claims 3-5 and 7-11 of the original application as filed.

Claims 15-17 are cancelled.

Claims 12, 13 and 14, which are directed to non-elected inventions, are cancelled.

2. Paragraph 3 of the Office Action: Claim Objection

The Examiner has objected to claim 16 because of the following informality: "5- g/l".

Claim 16 has been cancelled. Withdrawal of the corresponding objection is respectfully requested.

3. Paragraph 6 of the Office Action: Claim Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 1, 3-5 and 7-11 are rejected by the Examiner as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 1 has been cancelled, and claims 3-5 and 7-11 now depend on claim 2. Withdrawal of the corresponding rejection is thus respectfully requested.

4. Paragraph 8 of the Office Action: Claim Rejection under 35 U.S.C § 112, First Paragraph

Claims 1, 3-5 and 7-11 are rejected as containing subject matter which was not described in the Specification in such a way as to reasonably convey to the skilled person in the art that the Inventors, at the time the application was filed, had possession of the claimed invention.

Claim 1 has been cancelled, and claims 3-5 and 7-11 now depend on claim 2. Withdrawal of the corresponding rejection is thus respectfully requested.

5. Paragraph 9 of the Office Action: Claim Rejection under 35 U.S.C § 102(b)

Claims 2 and 15-17 are rejected as being anticipated by U.S. Patent No. 5,945,098 as is evidenced by the MSDS for glycine. This rejection is respectfully traversed.

The Examiner purports in particular that the transitional phrase “consisting essentially of” means that the stabilizing formulation of the invention may include components other than sugar alcohol, glycine and non-ionic detergent. The Examiner further urges that U.S. 5,945,098 teaches an aqueous IgG formulation comprising mannitol, glycine in a concentration of from about 0.1M to 0.3M (i.e. 7g/l to 21 g/l) and polysorbate 80, in a concentration of from 0.002% to 0.004% (i.e. 20 ppm to 40 ppm), and considers that these teachings anticipate the formulation claimed in the present invention.

Applicant respectfully disagrees for the following reasons.

The present invention concerns a formulation specifically drawn for stabilizing immunoglobulins G compositions under both liquid and lyophilized forms. As disclosed thoroughly in the Specification, the stabilizing properties of said formulation are provided by the specific combination of a sugar alcohol, glycine and a non-ionic detergent.

The transmittal phase “consisting essentially of” in claim 1 should be interpreted to define the composition on containing the recited materials, and potentially some other components, but only those “that do not materially affect the basic and novel characteristics” of the invention. *In re Hertz*, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original). In the present case, the Examiner’s attempted interpretation of the claims violates this fundamental and well established concept.

It unambiguously appears in the Specification of the present application that, besides the three recited main components, the stabilizing formulation of the invention might also include at least one other additive, such as a stabiliser or an excipient.

See the present application, in particular at page 5, lines 19-28:

“The stabilising formulation according to the invention can include, beside a sugar alcohol, glycine and a non-ionic detergent, at least one other additive. This additive can be a compound selected from the different categories of stabilisers classically used in the technical field of the invention, such as surface active agents, sugars and aminoacids, and a as well excipient added to the formulation in order to adjust, for example, the pH, the ionic strength, etc.”

Applicant however submits that the present application clearly defines the additives which could in no manner be used in the stabilizing formulation of the invention. For instance, it unambiguously appears that sugars provoking the onset of Maillard reactions are to be avoided.

See the present application, in particular at page 4, lines 2 to 6:

“Hydrolysis of sucrose into reducing sugars (fructose and glucose) which condense with amino residues of the lysine of IgG and of albumine, giving an instable Schiff’s base evolving into Maillard products (browning of the solution) is to be avoided”;

at page 4, lines 7 to 10

“moreover, some previously cited stabilisers, such as maltose or sucrose, cannot be used without risk in individuals suffering from renal failure and/or from diabetes”,

and at page 6, lines 18-22:

“the Applicant selected sugar alcohols on the basis of stability criteria at acidic pH of the conditioning of IgG compositions, thus avoiding the onset of Maillard reactions with immunoglobulins G”.

Similarly, the present application clearly indicates that stabilisers such as polyethylene glycol (PEG) are especially to be avoided when lyophilisation of the protein solutions is considered, since PEG is known to behave as a precipitating agent in such conditions.

See the present application, in particular at page 2, lines 14-20:

“some of these stabilisers, however, are known to be precipitating agents of proteins higher than about 100 kDa. Thus, the use of polyethylene glycol (PEG) 3000-6000 is redhibitory in the freezing phase leading to the lyophilisation of the corresponding protein compositions.”,

and at page 2, lines 30-31:

“Thus, it appears that the presence of PEG is undesirable”.

In view of these elements and according to the requirements defined in the MPEP 2111.03, Applicant therefore considers that the present application clearly defines the additives which are to be excluded from the stabilizing formulation of the invention. It therefore results that the transitional phrase “consisting essentially of”, as recited in claim 2, unambiguously excludes the addition of PEG in the stabilizing formulation of the invention.

Applicant further submits that all the stabilized formulations disclosed in U.S. 5,945,098 actually contain polyethylene glycol, which is purported to be important for ensuring the overall stability of the immunoglobulins compositions. See in particular column 6, lines 4 to 11, as well as examples I to V, which are all directed to aqueous IgG solutions containing polyethylene glycol:

“While PEG alone cannot provide a preparation as stable as those described herein, its presence is believe to be important to the overall stability of any immune globulin solution, including those of the present invention. Thus, if PEG is not already present in the starting source of immune globulin, a small amount (typically less than 0.2 gram %) should be included in the preparations of the invention.”

Therefore, U.S. 5,945,098 fails to disclose any stabilizing formulation which does not contain PEG, and therefore the reference fails to anticipate the stabilizing formulation of claim 2, or an immunoglobulin G composition according to claims 18-22, when those claims are properly analyzed.

In view of the above, Applicant considers that the subject matter of claim 2, and that of claims 3-5 and 7-11 is novel with respect to the disclosure of U.S. 5,945,098.

Withdrawal of the corresponding rejection is thus respectfully requested.

6. Paragraph 11 of the Office Action: Claim Rejection under 35 U.S.C. § 103(a)

In the pending Office Action, the Examiner rejects the claims as being obvious over a new combination of prior art references, namely U.S. 4,597,966 in view of EP 0392,717A1 and U.S. 2006/0246060A1, as evidenced by MSDS. Applicant respectfully disagrees and will demonstrate that the subject matter of claims 2 and 3-5 and 7-11 is not obvious over the teachings of U.S. 5,945,098, U.S. 4,957,966, EP 0392,717A1 and U.S. 2006/0246060A1, even when combined together.

As discussed previously, U.S. 5,945,098 fails to disclose any stabilising formulation which does not contain PEG. Applicant further submits that, as indicated in this patent, the disclosed formulations are intended for stabilizing liquid compositions only.

See U.S. 5,945,098, column 3, lines 62-64:

"the present invention advantageously provides a storage-stable liquid product, thus eliminating the inconvenience and expense of lyophilization and reconstitution."

This is confirmed by the Specification of the present application, which indicates that the stabilizing formulations provided by U.S. 5,945,098 are not suitable for lyophilisation since PEG induces the precipitation of immunoglobulins upon lyophilisation.

See the present application, in particular at page 2, lines 17-20:

“the use of polyethylene glycol (PEG) 3000-6000 is redhibitory in the freezing phase leading to the lyophilisation of the corresponding protein compositions.”

In view of these elements, and considering the fact that U.S. 4,957,966, EP 0392,717A1 and U.S. 2006/0246060A1 actually fail to provide any reason for removing PEG from the stabilising solution disclosed in U.S. 5,945,098, Applicant submits that one of ordinary skilled in the art would never have considered the teachings of U.S. 5,945,098 for preparing a stabilizing formulation to be used both in liquid and in lyophilized form, nor would he have had any reasonable expectation of success to prepare such a stabilizing formulation in view of the elements disclosed in U.S. 5,945,098.

U.S. 4,597,966 teaches a stabilizing formulation comprising IgG, histidine and glycine at a concentration of about 0.1M. This document explicitly discloses that the stabilizing effect results from the presence of histidine, which could be further combined with glycine.

See U.S. 4,597,966, in particular in column 4, lines 62-64:

“to that end the amino acid histidine is utilized as a stabilising agent. Preferably, histidine is used together with glycine”

U.S. 4,597,966 demonstrates that the described formulation of histidine and glycine allows the stabilization of gamma globulins under liquid or lyophilised forms without generating dimers or aggregates. It however clearly appears that no further additive is encompassed by the formulation described in U.S. 4,597,966, and that this patent fails to disclose or even suggest that the stabilizing formulation may comprise any additional compound, such as, for instance, mannitol and non-ionic detergent, as claimed in the present application.

See U.S. 4,597,966, in particular in column 4, lines 30-37:

“to that end, a particularly preferred stabilized, sterile gamma globulin composition, exhibiting substantially no anticomplement activity, comprises an aqueous solution

containing a pharmacologically effective concentration of gamma globulin, histidine in a concentration sufficient to inhibit gamma globulin aggregation, and glycine in a concentration of about 0.05M to about 0.5M."

EP 0392,717 teaches pharmaceutical formulations for stabilizing immunoglobulin conjugates, which contain mannitol and glycine. EP 0392,717 demonstrates in particular that a formulation containing an immunoglobulin conjugate, glycine and mannitol in a 1:1:1 weight ratio reduces the aggregation of said conjugates upon liquid storage or lyophilisation (see tables I and II).

First of all, Applicant respectfully submits that one of ordinary skill in the art would never have reasonably considered the teachings of EP 0392,717 for preparing a formulation intended for the stabilization of immunoglobulins G. It indeed clearly appears that EP 0392,717 only concerns the stabilization of immunoglobulin conjugates resulting from the reaction of a vinca hydrazide, the formula of which is disclosed at page 3, with an oxidized glycoprotein.

See EP 0392,717, in particular at page 4, lines 33-36:

"that is to say, the present invention will serve to stabilize against aggregation a formulation containing an immunoglobulin conjugate of an indol-dihydroindole alkaloid and a glycoprotein regardless of the chemical linkage employed between the two portions".

It is however well known in the art that stabilizing conditions defined for immunoglobulin conjugates are directly dependent upon the nature of the chemical residue which is linked to the immunoglobulin. Therefore, the stabilizing conditions of non-conjugated immunoglobulins (such as immunoglobulins G) could in no manner be inferred from the results obtained with the conjugated immunoglobulins disclosed in EP 0392,717.

Further, EP 0392,717 specifically discloses that the stabilizing formulation for conjugated immunoglobulins results in the reduction of the amount of agglomerated particles to about 13% after 2 months storage at 25°C (see table I). Considering that, as disclosed explicitly in the present application, the standards of the European Pharmacopeia for IgG compositions are set to at most 3% of polymers (i.e. of aggregates, see the present application, page 1, line 25) after 6 months storage at room temperature, Applicant submits that one of ordinary skill in the art would

never have reasonably considered the teachings of EP 0392,717, nor would he have had a reasonable chance of success in preparing the stabilizing formulation of the invention in view of EP 0392,717.

See the present application in particular at page 7, lines 25-29:

“it is noted that the storage of the IgG compositions in liquid form during 6 months at room temperature generates an amount of polymers well below the standards set in the European Pharmacopeia (3%), that is to say less than about 0.3%”

Finally, Applicant submits that EP 0392,717 clearly indicates that the disclosed stabilising formulation is exclusively composed of immunoglobulin conjugates, glycine and mannitol, and therefore fails to teach or to suggest any stabilizing formulation comprising further additives.

U.S. 2006/0246060 teaches stable aqueous pharmaceutical formulations for huC242-DM1, i.e. for an immunoconjugate formed by the linkage of an antibody to a cytotoxic agent, as well as stable frozen formulations for the monoclonal antibody C242. This application discloses in particular formulations containing a buffer and a polyol (preferably sucrose or trehalose), and optionally a non-ionic surfactant such as polysorbate.

As disclosed in U.S. 2006/0246060, in particular at page 2, right column, lines 42-43, as well as at page 3, lines 3-5, sucrose is considered as an essential component of the stabilizing formulation since it is purported to act as a tonicifier, to stabilize the monoclonal antibody, and to serve as a bulking agent as well as a cryoprotectant during the lyophilisation cycle. On the contrary, the surfactant is only purported to confer additional stability to the liquid storage solutions but is clearly not included in formulations intended for lyophilisation storage.

See U.S. 2006/0246060, at page 1, left column, line 61 to right column, line 3:

“further contemplated in the above formulation is the presence of a stabilizing surfactant, in order to confer additional stability to the starting solutions of each product such that they may not require storage under frozen or freeze-dried conditions.”,

and at page 3, right column, lines 5-8:

*“however, it was determined that the addition of a surfactant, such as Pluronic F68, should be considered in the case where a **solution** dosage form was desired” (emphasize added).*

U.S. 2006/0246060 further fails to teach or to suggest any stabilizing formulation comprising further additives, such as glycine or mannitol, for instance.

As discussed above, each of the documents U.S. 4,957,966, EP 0392,717A1 and U.S. 2006/0246060A1 actually disclose a very specific stabilizing formulation, the properties of which clearly rely on the limited number of compounds used. In view of these teachings, Applicant submits that a person skilled in the art would therefore have had no reasonable incentive to combine the different formulations.

Even assuming arguendo that a person skilled in the art would have combined the teachings of the cited documents (which Applicant denies), the resulting stabilising formulation would have inevitably comprised histidine, glycine, mannitol and sucrose (a sugar which is clearly excluded from the stabilizing formulation of the invention), since all these elements are purported to be essential for stabilisation in U.S. 4,957,966, EP 0392,717A1 and U.S. 2006/0246060A1. On the contrary, one of ordinary skill in the art would have clearly avoided the addition of non-ionic surfactants since U.S. 2006/0246060 indicates that such surfactants are not appropriate for stabilization under lyophilised forms. Therefore, one of ordinary skill in the art would therefore have had no reasonable expectation of success to prepare the stabilizing formulation for immunoglobulins G compositions of the present invention.

The subject matter of claim 2, as well as that of claims 3-5 and 7-11 is thus non-obvious over the teachings of U.S. 5,945,098, U.S. 4,957,966, EP 0392,717A1 and U.S. 2006/0246060A1, even when combined together.

Withdrawal of the corresponding rejection is thus respectfully requested.

In view of the above amendments, Applicant believes the pending application is in condition for allowance.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant respectfully petitions for a two (2) month extension of time for filing a reply in connection with the present application, and the required fee of \$490.00 is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson Reg. No. 30,330 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By 

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